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(71) Applicant *(for all designated States except US)*: **BIOCON INDIA LIMITED** [IN/IN]; 20th K.M. Hosur Road, Hebbagodi, Bangalore 561 229 (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **MATHEW, Joy** [IN/IN]; 20th K.M. Hosur Road, Hebbagodi, Bangalore 561 229, Karnataka (IN). **GANESH, Sambasivam** [IN/IN]; 20th K.M. Hosure Road, Hebbagodi, Bangalore 561 229, Karnataka (IN).

(74) Agents: **ANAND, Pravin** et al.; Anand and Anand, Advocates, B-41, Nizamuddin East, New Dehli 110 013 (IN).

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(54) Title: FORM V CRYSTALLINE [R-(R*,R*)]-2-(4-FLUOROPHENYL)-ß,$G(D)-DIHYDROXY-5-(1-METHYLETHYL)-3-PHENYL-4-[(PHENYLAMINO)CARBONYL]-1H-PYRROLE-1- HEPTANOIC ACID HEMI CALCIUM SALT. (ATORVASTATIN)

(57) Abstract: A novel crystalline form of [R-(R*,R*)]-2-(4-fluorophenyl)-ß,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1- heptanoic acid hemi calcium salt designated as Form V is characterized by its X-ray powder diffraction and/or solid state NMR is described, as well as methods for the preparation which is useful as an agent for treating hyperlipidemia and hypercholesterolemia.

Form V crystalline [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt. (ATORVASTATIN)

FIELD OF THE INVENTION

The present invention relates to a process for the production of form V of [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (ATORVASTATIN). The present invention further relates to a method of production of form V of [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt and its isolation. This novel crystalline form of atorvastatin is useful as a pharmaceutical agent, as an inhibitor of the enzyme 3-hydroxy-3 methylglutaryl-coenzyme.A reductase (HMG-CoA reductase) and is thus useful as a hypolipidemic and hypocholesterolemic agent.

BACKGROUND OF THE INVENTION

Atorvastatin calcium, a synthetic HMG-CoA reductase inhibitor, is used for the treatment of hyperlipidemia and hypercholesterolemia, both of which are risk factors for arteriosclerosis and coronary heart disease.

United States Patent Number 4,681,893, which is herein incorporated by reference, discloses certain intermediates used in the synthesis of atorvastatin. United States Patent Number 5,273,995, which is herein incorporated by reference, discloses the enantiomer having the R form of the

ring-opened acid of [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid. United States Patent Numbers 5,003,080; 5,097,045; 5,103,024; 5,124,482; 5,149,837; 5,155,251; 5,216,174; 5,245,047; 5,248,793; 5,280,126; 5,397,792; and 5,342,952, which are herein incorporated by reference, disclose various processes and key intermediates for preparing atorvastatin.

Atorvastatin is prepared as its calcium salt, i.e., [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (2:1). The process by which atorvastatin is produced should be

(i) easily scaled up for commercial production

(ii) The product should be in a form that is readily filterable and easily dried.

(iii) The product is stable for extended periods of time without the need for specialized storage conditions.

The processes in the above United States Patents disclose amorphous atorvastatin which has unsuitable filtration and drying characteristics for large-scale production and must be protected from heat, light, oxygen, and moisture.

To overcome the above disadvantages, the present invention provides atorvastatin in a new crystalline form designated Form V. Form V atorvastatin has different physical characteristics compared to the previous crystalline or amorphous product.

SUMMARY OF THE INVENTION

Accordingly, the present invention is directed to crystalline Form V atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the 2θ, d-spacings, and relative intensities measured on a STOE/STADI-P X-ray powder diffractometer with germanium monochromated Cu K alpha 1(L =1.54056 Angstroms) Siemens D-500 diffractometer with CuK. Radiation:

2θ-OBS	2θ-CALC	D-OBS	Relative Intensity(%)
5.340	5.340	16.5350	7.9
8.618	8.611	10.2525	23.1
8.724	8.697	10.1282	25.2
8.950	8.946	9.8727	30.1
9.819	9.828	9.0004	28.7
10.094	10.063	8.7564	20.0
11.335	11.337	7.8004	21.0
16.673	16.671	5.3128	100.0
17.955	17.947	4.9363	19.3
19.161	19.132	4.6283	43.3
21.479	21.479	4.1338	69.2
22.561	22.568	3.9378	38.3
23.154	23.122	3.8384	43.2
23.576	23.588	3.7707	33.7
24.324	24.309	3.6563	6.6
24.560	24.559	3.6217	10.5

26.268	26.295	3.3900	8.1
28.224	28.217	3.1593	9.8
28.804	28.781	3.0970	9.9
29.199	29.195	3.0560	21.7
30.370	30.371	2.9408	10.8
31.893	31.909	2.8037	12.3
37.356	37.337	2.4053	10.3

Further, the present invention is directed to crystalline Form V atorvastatin and hydrates thereof characterized by the following solid-state ^{13}C nuclear magnetic resonance spectrum wherein chemical shift is expressed in parts per million measured on a Bruker DRX-500MHz spectrometer:

Assignment (8kHz)	Chemical Shift
Spinning Side Band	59.64
Spinning Side Band	157.9
Spinning Side Band	161.59
C12 or C25	183.4
C12 or C25	177.6
C16	166.4 159.5
Aromatic Carbons C2-5, C13-C18, C19-24, C27-C32	136.4 134.4 130.2 128.8 127.5 122.7

	120.1 117.0 112.9
C8, C10	72.3 69.5 67.3 64.0
Methylene Carbons C6, C7, C9, C11	46.5 40.5
C33	25.5 24.0
C34	20.42

The present invention further relates to a process for the preparation of Form V atorvastatin Calcium and hydrates thereof which comprises

(i) stirring heterogeneous mixture of atorvastatin calcium in a mixture of water and absolute ethanol;

(ii) filtering to get the solid;

(iii) drying to get Form V atorvastatin calcium.

The ratio of water and absolute alcohol is in the range of 3 :1 to 8:1, preferably 4.67 : 1.

Stirring is carried at 25 - 50 deg centigrade, preferably 40 deg centigrade.

The stirring is carried for 10 - 25 hrs, preferably 17 hours.

The final product is dried in vacuum tray drier.

BRIEF DESCRIPTION OF THE ACCOMPANYING DRAWINGS

The invention is further described by the following non-limiting examples which refer to the accompanying Figures 1 to 4, short particulars of which are given below.

Figure 1:

Diffractogram of heterogeneous mixture of atorvastatin calcium. The horizontal axis represents 2θ and the vertical axis corresponds to peak intensity.

Figure

Diffractogram of Form V atorvastatin. The horizontal axis represents 2θ and the vertical axis corresponds to peak intensity.

Figure 3:

The solid state ^{13}C nuclear magnetic resonance spectrum of heterogeneous mixture of atorvastatin calcium.

Figure 4:

The solid state ^{13}C nuclear magnetic resonance spectrum of Form V atorvastatin calcium.

DETAILED DESCRIPTION OF THE INVENTION

Crystalline Form V atorvastatin may be characterized by its X-ray powder diffraction pattern and/or by its solid state nuclear magnetic resonance spectra (NMR).

X-RAY POWDER DIFFRACTION - Form V Atorvastatin

Form V atorvastatin was characterized by its X-ray powder diffraction pattern. Thus, the X-ray diffraction pattern of Form V atorvastatin was

measured germanium monochromated Cu K alpha 1(L =1.54056 Angstroms)

Equipment

STOE/STADI-P powder diffractometer with an IBM-PC compatible interface , STOE software = DIFFRAC AT (SOCABIM 1986, 1992). CuKa radiation (20 mA, 40 kV, k = 1.5406 A) slits I and II at 10) electronically filtered by the Kevex Psi Peltier Cooled Silicon [Si(Li)]Detector (Slits: III at 10 and IV at 0.150).

Methodology

The silicon standard is run each day to check the X-ray tube alignment. X-ray generator; sealed tube; 30KV; 5mA Curved PSD detector in the transmission mode, step size 0.03 degrees 2theta range 3-60 in two frames of 5 minutes exposure each per frame. Raw sample mounted on the transmission block on mylar (x-ray proof) film and rotated to avoid orientation effects. Table 1 lists the 2θ, d-spacings, and relative intensities of all lines in the ungrounded sample with a relative intensity for crystalline Form V atorvastatin. It should also be noted that the computer-generated unrounded numbers are listed in this table.

TABLE 1. Intensities and Peak Locations of All Diffraction Lines With Relative Intensity for Form V Atorvastatin

2θ-OBS	2θ-CALC	D-OBS	Relative Intensity(%)
5.340	5.340	16.5350	7.9

8.618	8.611	10.2525	23.1
8.724	8.697	10.1282	25.2
8.950	8.946	9.8727	30.1
9.819	9.828	9.0004	28.7
10.094	10.063	8.7564	20.0
11.335	11.337	7.8004	21.0
16.673	16.671	5.3128	100.0
17.955	17.947	4.9363	19.3
19.161	19.132	4.6283	43.3
21.479	21.479	4.1338	69.2
22.561	22.568	3.9378	38.3
23.154	23.122	3.8384	43.2
23.576	23.588	3.7707	33.7
24.324	24.309	3.6563	6.6
24.560	24.559	3.6217	10.5
26.268	26.295	3.3900	8.1
28.224	28.217	3.1593	9.8
28.804	28.781	3.0970	9.9
29.199	29.195	3.0560	21.7
30.370	30.371	2.9408	10.8
31.893	31.909	2.8037	12.3
37.356	37.337	2.4053	10.3

SOLID STATE NUCLEAR MAGNETIC RESONANCE (NMR)

Methodology

High resolution 13C spectra were obtained using high power proton decoupling and cross polarization with magic angle spinning at approximately 5 (8)kHz. The magic angle was adjusted using the 79Br signal of KBr by detecting the side bands as described by Frye et. Al. (J. Mag. Res., 1992, 48, 125). Approximately 150-200mg of the sample was packed into a canistor design rotor was used for each experiment. Chemical shifts was referred op the methine carbon of an external sample of admantane taken as 37.8 ppm with reference to tetrakis trimethylsilyl silane. Table 2 shows the solid-state NMR spectrum for crystalline Form V atorvastatin.

TABLE 2. Carbon Atom Assignment and Chemical Shift for Form V

Assignment (8kHz)	Chemical Shift
Spinning Side Band	59.64
Spinning Side Band	157.9
Spinning Side Band	161.59
C12 or C25	183.4
C12 or C25	177.6
C16	166.4 159.5
Aromatic Carbons C2-5, C13-C18, C19-24, C27-C32	136.4 134.4 130.2 128.8 127.5

	122.7 120.1 117.0 112.9
C8, C10	72.3 69.5 67.3 64.0
Methylene Carbons C6, C7, C9, C11	46.5 40.5
C33	25.5 24.0
C34	20.42

Crystalline Form V atorvastatin of the present invention can exist in anhydrous forms as well as hydrated forms. In general, the hydrated forms are equivalent to unhydrated forms and are intended to be encompassed within the scope of the present invention.

The present invention also provides a process for the preparation of crystalline Form V atorvastatin which comprises exposing atorvastatin to a high relative humidity under conditions which yield crystalline Form V atorvastatin.

The precise conditions under which Form V of crystalline atorvastatin is formed may be empirically determined and it is only possible to give a method, which has been found to be suitable in practice.

Crystalline Form V atorvastatin may be prepared by crystallization under controlled conditions. In particular, it can be prepared either from an

aqueous solution of the corresponding basic salt such as, an alkali metal salt, for example, lithium, potassium, sodium, and the like; ammonia or an amine salt; preferably, the sodium salt by addition of a calcium salt, such as, for example, calcium acetate and the like, or by suspending heterogeneous mixture of atorvastatin in water.

In general, the use of a hydroxylic co-solvent such as, for example, a lower alcohol, for example methanol and the like, is preferred. The following non-limiting examples illustrate the inventors' preferred methods for preparing the compounds of the invention.

EXAMPLE 1

Crystalline [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt

(Form V Atorvastatin)

A heterogeneous mixture of Atorvastatin Calcium (10 g) stirred in a mixture of water and absolute ethanol (140 ml: 30 ml respectively) at 40 deg centigrade for 17 hrs. The product is filtered and sucked dried. The filtered semi dried product is dried in a vacuum tray drier (650 mm Hg) for 17 hrs to get 9 g of finished product.

X-ray powder diffraction pattern (Figure 2 as shown in the accompanied drawings) demonstrates the novel crystalline nature of the product - Form V as against the heterogeneous nature of the starting material (Figure 1 as shown in the accompanied drawings)

Solid state ^{13}C nuclear magnetic resonance spectrum of Form V atorvastatin calcium (Figure 4 as shown in the accompanied drawings) was compared with that of the heterogeneous mixture of form (Figure 3 as shown in the accompanied drawings) to confirm the observations.

Example 2

Indexing of Form V Atorvastatin Calcium

The indexing of the powder diffraction pattern of the Form V atorvastatin calcium was carried using THEOR90; in the suite of CRYSFIRE, a package for indexing powder x-ray diffraction pattern yielded the following results -

Total number of lines = 24
a = 11.338(3) A^o; $\alpha = 83.07(7)^o$
b = 11.058(4) A^o; $\beta = 73.47(11)^o$
c = 17.249(11) A^o; $\gamma = 68.12(4)^o$
V = 1923.83 A^{o3}

We claim:

1. Crystalline Form V atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the 2θ, d-spacings, and relative intensities measured using CuK radiation:

2θ-OBS	2θ-CALC	D-OBS	Relative Intensity(%)
5.340	5.340	16.5350	7.9
8.618	8.611	10.2525	23.1
8.724	8.697	10.1282	25.2
8.950	8.946	9.8727	30.1
9.819	9.828	9.0004	28.7
10.094	10.063	8.7564	20.0
11.335	11.337	7.8004	21.0
16.673	16.671	5.3128	100.0
17.955	17.947	4.9363	19.3
19.161	19.132	4.6283	43.3
21.479	21.479	4.1338	69.2
22.561	22.568	3.9378	38.3
23.154	23.122	3.8384	43.2
23.576	23.588	3.7707	33.7
24.324	24.309	3.6563	6.6
24.560	24.559	3.6217	10.5
26.268	26.295	3.3900	8.1
28.224	28.217	3.1593	9.8
28.804	28.781	3.0970	9.9
29.199	29.195	3.0560	21.7

30.370	30.371	2.9408	10.8
31.893	31.909	2.8037	12.3
37.356	37.337	2.4053	10.3

2. Crystalline Form V atorvastatin and hydrates thereof characterized by the following solid-state ^{13}C nuclear magnetic resonance spectrum wherein chemical shift is expressed in parts per million:

Assignment Chemical Shift

Assignment (8kHz)	Chemical Shift
Spinning Side Band	59.64
Spinning Side Band	157.9
Spinning Side Band	161.59
C12 or C25	183.4
C12 or C25	177.6
C16	166.4 159.5
Aromatic Carbons C2-5, C13-C18, C19-24, C27-C32	136.4 134.4 130.2 128.8 127.5 122.7 120.1 117.0 112.9
C8, C10	72.3

	69.5 67.3 64.0
Methylene Carbons C6, C7, C9, C11	46.5 40.5
C33	25.5 24.0
C34	20.42

3. A process for the preparation of Form V crystalline atorvastatin Calcium and hydrates thereof which comprises

(iv) stirring heterogeneous mixture of atorvastatin calcium in a mixture of water and absolute ethanol;

(v) filtering to get the solid;

(vi) drying to get Form V atorvastatin calcium.

4. A process of claim 3 wherein the ratio of water and absolute ethanol is in the range of 3:1 to 8 :1.

5. A process of claim 4, wherein the ratio of water and alcohol is 4.67: 1.

6. A process of claim 3, wherein the stirring is carried out at 25 - 50 deg centigrade.

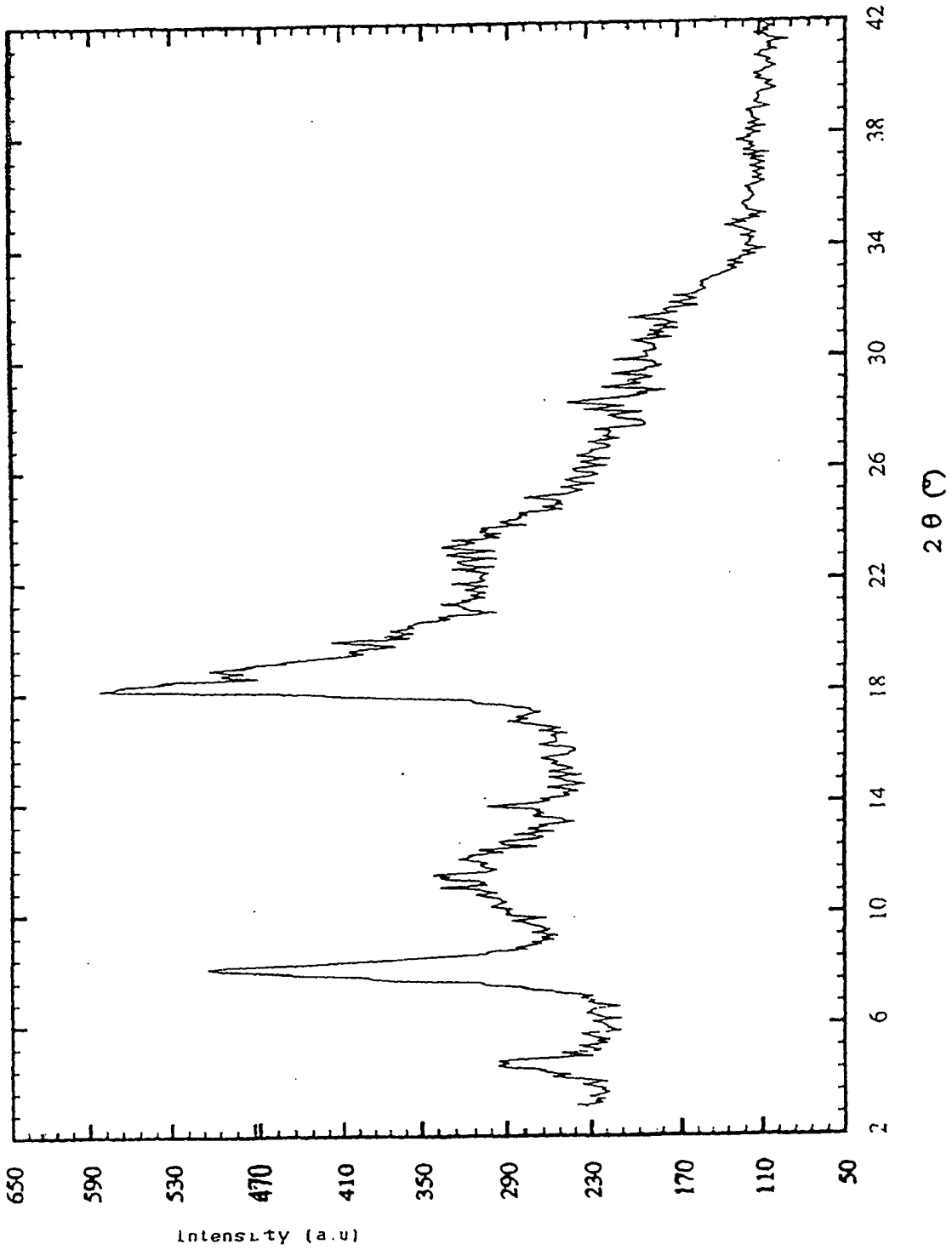
7. A process of claim 6, wherein the stirring is carried out at 40 deg centigrade.

8. A process of claim 3, wherein the stirring is carried out for 10 - 25 hrs.

9. A process of claim 8, wherein the stirring is carried out for 17 hours.

10. A process of claim 3, wherein the final product is dried in vacuum tray drier.

Figure 1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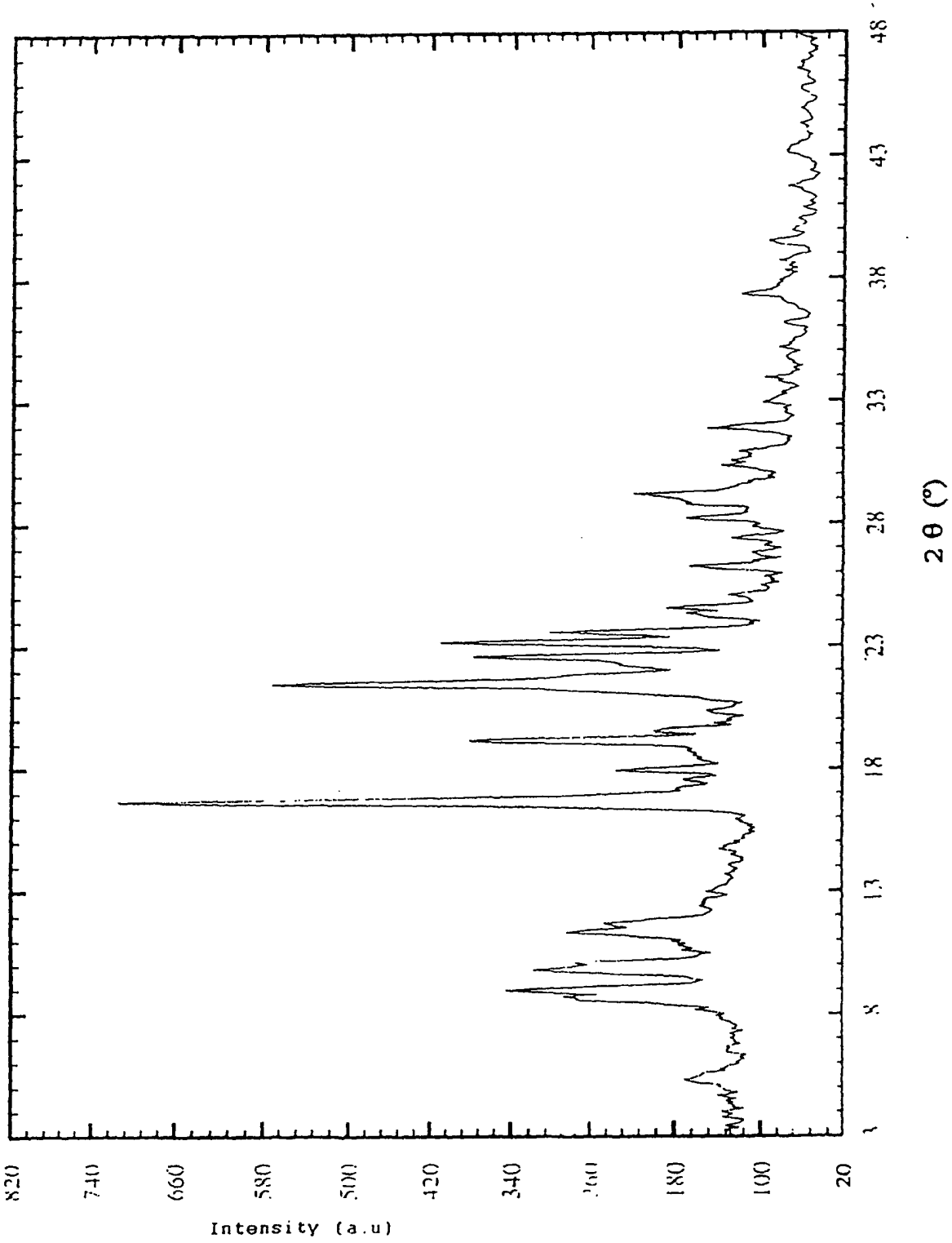
6
10
14
18
22
26
30
34
38
42
2 θ (°)

Figure 2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23
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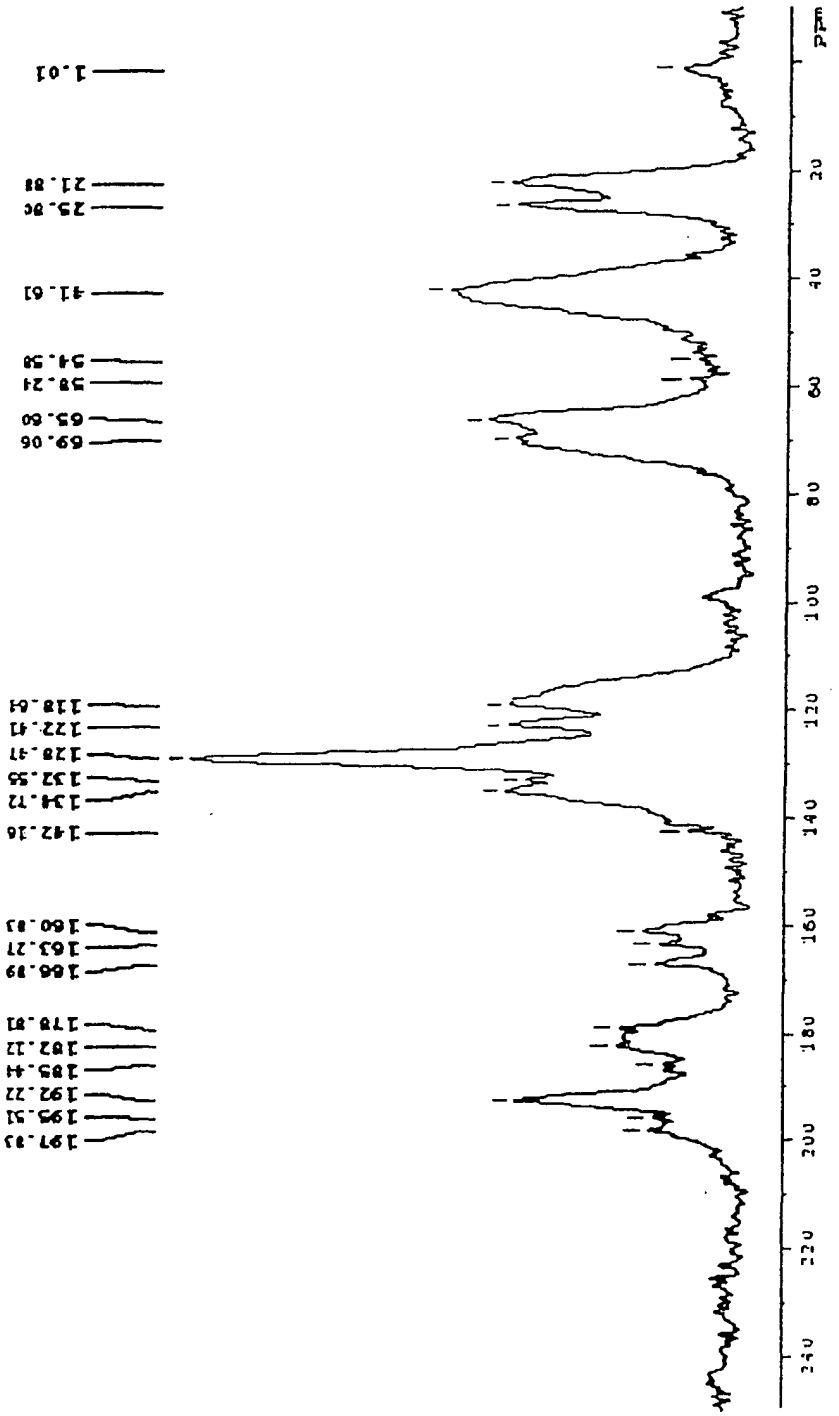
13
8
3

Figure 3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134.72
142.16
160.83
163.27
166.89
178.81
182.12
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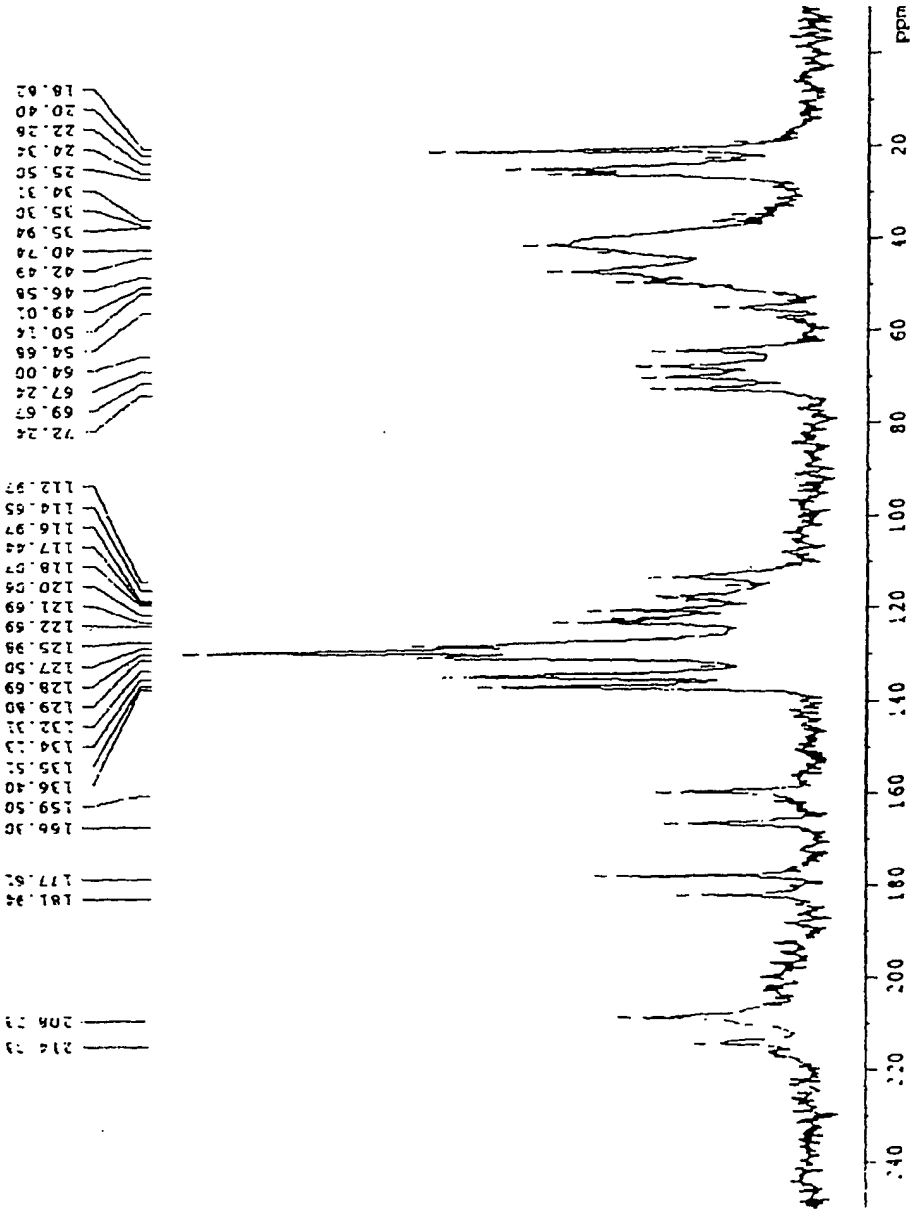
240

Figure 4



INTERNATIONAL SEARCH REPORT

Ir onal Application No
PCT/IN 01/00006

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D207/34 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 03959 A (WARNER LAMBERT CO ;BRIGGS CHRISTOPHER A (US); JENNINGS REX ALLEN () 6 February 1997 (1997-02-06) page 20, line 19 -page 22, line 11; figures 1,4 ---	1-10
E	WO 01 36384 A (TEVA PHARMA ;AYALON ARI (IL); NIDDAM VALERIE (IL); ROYTBLAT SOFIA) 25 May 2001 (2001-05-25) the whole document ---	1-10
A	WO 97 03958 A (WARNER LAMBERT CO ;MCKENZIE ANN T (US)) 6 February 1997 (1997-02-06) the whole document ---	1-10
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
13 September 2001	20/09/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Von Daacke, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In ɔnal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 04543 A (WARNER LAMBERT CO ;BUTLER DONALD EUGENE (US); JACKS THOMAS ELLIOTT) 5 February 1998 (1998-02-05) example 8	2
A	US 5 397 792 A (BUTLER DONALD E ET AL) 14 March 1995 (1995-03-14) cited in the application example 1	3-10

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IN 01/00006

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9703959 A	06-02-1997	AU 725424 B	12-10-2000
		AU 6484296 A	18-02-1997
		BG 102187 A	30-10-1998
		BR 9609872 A	23-03-1999
		CA 2220018 A	06-02-1997
		CN 1190955 A	19-08-1998
		CZ 9800121 A	14-10-1998
		EE 9800015 A	17-08-1998
		EP 0848705 A	24-06-1998
		HR 960339 A	30-04-1998
		HU 9900678 A	28-07-1999
		IL 122118 A	14-07-1999
		JP 11509230 T	17-08-1999
		NO 980207 A	16-01-1998
		PL 324496 A	25-05-1998
		SK 6298 A	07-10-1998
		US 5969156 A	19-10-1999
WO 0136384 A	25-05-2001	NONE	
WO 9703958 A	06-02-1997	AU 725368 B	12-10-2000
		AU 6484196 A	18-02-1997
		BG 102186 A	30-10-1998
		BR 9610567 A	06-07-1999
		CA 2220458 A	06-02-1997
		CN 1190957 A	19-08-1998
		CZ 9800123 A	17-06-1998
		EE 9800016 A	17-08-1998
		EP 0848704 A	24-06-1998
		HR 960313 A	30-04-1998
		HU 9901687 A	28-10-1999
		IL 122162 A	14-07-1999
		JP 11509229 T	17-08-1999
		NO 980208 A	16-01-1998
		PL 324532 A	08-06-1998
		SK 5998 A	06-05-1998
		TW 401399 B	11-08-2000
		US 6121461 A	19-09-2000
WO 9804543 A	05-02-1998	AU 3515497 A	20-02-1998
		EP 0915866 A	19-05-1999
		HU 9904348 A	28-04-2000
		JP 2000515882 T	28-11-2000
		TR 9900191 T	21-04-1999
		US 5998633 A	07-12-1999
US 5397792 A	14-03-1995	US 5342952 A	30-08-1994
		US 5298627 A	29-03-1994
		US 5446054 A	29-08-1995
		US 5470981 A	28-11-1995
		US 5510488 A	23-04-1996
		US 5489691 A	06-02-1996
		US 5489690 A	06-02-1996
		AT 156127 T	15-08-1997
		AU 677047 B	10-04-1997
		AU 6274294 A	26-09-1994
		CA 2155952 A	15-09-1994
		CZ 285554 B	15-09-1999

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IN 01/00006

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5397792 A		CZ 285555 B	15-09-1999
		CZ 9800479 A	11-08-1999
		CZ 9502206 A	13-12-1995
		DE 69404632 D	04-09-1997
		DE 69404632 T	29-01-1998
		DK 687263 T	16-02-1998
		EP 0687263 A	20-12-1995
		ES 2108435 T	16-12-1997
		FI 954073 A	30-08-1995
		GR 3024784 T	30-01-1998
		HU 75034 A	28-03-1997
		JP 8507521 T	13-08-1996
		NO 953438 A	01-11-1995
		NO 994708 A	22-11-1999
		NO 20000910 A	13-03-2000
		NZ 262830 A	26-11-1996
		RU 2138497 C	27-09-1999
		SK 109095 A	06-12-1995
		SK 281110 B	11-12-2000
		WO 9420492 A	15-09-1994